REMARKS

Election/Restrictions:

Applicants thank the Examiner for withdrawing the restriction between invention Groups I and II. Per the Office action, claims 80, 89, 103, 109, and 111 are pending and claims 112-118 are withdrawn.

Claim Rejections

35 U.S.C. § 112

Claims 80, 89, 103, 109, and 111 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Office action alleges that "[t]he specification does not describe the claimed derivatives of salicylic acid and acetylsalicylic acid . . . [because] the specification does not describe [a] reasonable number of pharmaceutically acceptable salts of all the claimed non-steroidal anti-inflammatory drugs (NSAID)." Page 4 of the Office action mailed 8 May 2006.

Applicants respectfully disagree. A written description of an invention involving a chemical genus requires a precise definition, such as by structure, formula ... of the claimed subject matter sufficient to distinguish it from other materials. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997, emphasis supplied). Further, in order to adequately describe a claimed genus, the specification need not describe all of the species that the genus encompasses. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (emphasis added). Rather, all that is required is description of a representative number and variety of species. *Lilly*, 119 F.3d at 1569; *Amgen*, 927 F.2d at 1213-14; *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998).

Applicants respectfully submit that they have provided a description of the claimed non-steroidal anti-inflammatory drugs that both describes a representative number and variety of the claimed non-steroidal anti-inflammatory drugs and is sufficient to

distinguish the claimed non-steroidal anti-inflammatory drugs from others. Specifically, at pages 9-11 of the specification, Applicants describe a significant number of non-steroidal anti-inflammatory drugs including: salicylic acid, acetylsalicylic acid, sulindac sulfide; sulindac sulfone; sulfasalazine, sodium salicylate; ibuprofen; celecoxib; rofecoxib; flufenamic acid; indomethacin; nabumetone; and naproxen. Indeed, Applicants provide chemical designations and molecular weights for celecoxib, benzenesulfonamide, rofecoxib, flufenamic acid, indomethacin, nabumetone, naproxen, and sulfasalazine. In addition, Applicants provide other examples of non-steriodal anti-inflammatory drugs within the scope of the claims. For example, Applicants provide examples of a substituted salicylic acid, *e.g.* acetylsalicylic acid, and of a pharmaceutically acceptable salt, *e.g.* sodium salicylate. Applicants further provide an example of a combination of non-steroidal anti-inflammatory agents. Specifically, at paragraphs 113 and 114 Applicants disclose examples of kits for reducing the size or improving the appearance of a closed wound, wherein the kits include acetylsalicylic acid and ibuprofen (paragraph 0113), or 2%-5% salicylic acid, 2%-5% acetylsalicylic acid, and 2%-5% ibuprofen (paragraph 0114). For all of these reasons, Applicants respectfully submit that they have described a representative number and variety of non-steroidal anti-inflammatory agents useful in compositions of the present invention and thus have satisfied the written description requirement of 35 U.S.C. § 112, first paragraph. This rejection is overcome and Applicants respectfully request it be withdrawn.

35 U.S.C. § 103

The Office action mailed 8 May 2006 rejects each of claims 80, 89, 103, 109, and 111 as allegedly unpatentable under 35 U.S.C. § 103(a) in view of one or more of JP 08-259465, US 6,652,856, US 6,521,271, US 4,244,948, US 5,552,162, and DE 27 07 537, alone or in combination.

Applicants respectfully disagree that any of these references, either alone or in combination, render the invention of claims 80, 89, 103, 109, and 111 obvious.

Specifically, Applicants respectfully disagree that any of these references establish a *prima facie* case of obviousness. According to section 2143 of the MPEP:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
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> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed more fully below, none of the cited references establish a *prima facie* case of obviousness. First, one of ordinary skill in the art would not be motivated to modify the teachings of any of the references nor do the cited references contain any such suggestion or motivation. Second, even if there were some motivation or suggestion to modify the teachings of the cited references, there is no reasonable expectation of success. Third, none of the cited references teach or suggests all of the claim limitations.

JP 08-259465 ('465)

Claims 80, 89, 103, 109, and 111 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over JP-08-259465 ('465). In particular, the Office action alleges that "JP '465 suggests the treatment of keloid or hypertrophic scar using NSAID." Page 5 of the Office action mailed 8 May 2006.

Applicants respectfully disagree that JP '465 renders the inventions of claims 80, 89, 103, 109, and 111 *prima facie* obvious under § 103. First, there is no suggestion or motivation to modify the teaching of JP '465 to arrive at the invention of claims 80, 89, 103, 109, and 111. Specifically, the claims are directed to a composition *consisting essentially of* a pharmaceutically acceptable carrier and a non-steroidal anti-inflammatory agent. In contrast, JP '465 is directed to a *combination* of "a nonsteroidal (*sic*) anti-inflammatory agent and sodium cromoglycate." (page 1, PURPOSE). JP '465

does not provide any motivation or suggestion to use the nonsteroidal anti-inflammatory agent alone in a composition for treating a skin disease. Indeed, JP '465 considers whether a non-steroidal anti-inflammatory agent *by itself* would be effective at treating skin diseases but concludes the results for use of the non-steroidal anti-inflammatory agent by itself are "hardly acceptable." Thus, JP '465 not only fails to provide any suggestion or motivation to modify the combination taught in JP '465 by using the ingredients individually; JP '465 teaches away from doing so.

More specifically, JP '465 examined whether a composition containing either a nonsteroidal anti-inflammatory agent alone would be effective at controlling erythema.[1] (*See* paras. [0032-0033], [0038-0039]). According to JP '465, a higher percentage of erythema control correlates with a more effective treatment of a skin disease. JP '465 teaches that in "external preparations . . . which contain a non steroid anti-inflammatory agent . . . *independently,* effectiveness was hardly accepted." (para. [0041]) (emphasis added). Indeed, the reported results indicate that when used alone, a non-steroidal anti-inflammatory agent is "hardly accepted" and not effective because by itself, the nonsteroidal anti-inflammatory agent typically achieved erythema control levels of only 2-4%. In contrast, the *combination* of a non-steroidal anti-inflammatory agent and sodium dichromoglycate achieved erythema control levels of 38-42%. Thus, JP '465 teaches that the *combination* of a non-steroidal anti-inflammatory agent and sodium cromoglycate is effective for treating a skin condition. JP '465 does not provide any suggestion or motivation for using a nonsteroidal anti-inflammatory agent by itself to treat a skin disease. Rather, JP '465 teaches such a composition would be ineffective and "hardly accepted."

The experiments reported in JP '465 further demonstrate that one of ordinary skill in the art would not have a reasonable expectation of success at achieving the result of the claimed invention, *i.e.* reducing the size or improving the appearance of a closed wound, because JP '465 reports that erythema control achieved using a nonsteroidal anti-inflammatory agent alone "was hardly accepted." Indeed, the reported erythema

[1] Stedman's Medical Dictionary defines "erythema" as "redness of the skin caused by dilatation and congestion of the capillaries, often a sign of inflammation or infection."

control levels for use of the nonsteroidal anti-inflammatory agent itself were negligible, only 2-4%.

Moreover, JP '465 does not teach each and every element of claims 80, 89, 103, 109, and 111. Specifically, JP '465 does not teach the types of closed wound recited in the claims. As such, JP '465 does not satisfy any of the three requirements for establishing even a *prima facie* case of obviousness. This ground of rejection is overcome for claims 80, 89, 103, 109, and 111. Applicants respectfully request it be withdrawn.

US 6,652,856 ('856) in view of US 5,552,162 ('162)

Claims 80, 89, 103, 109, and 111 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over '856 in view of '162. Specifically, the Office action alleges that "US '856 suggests the treatment of keloid and hypertrophic scar using NSAID." Page 6 of the Office action mailed 8 May 2006.

Applicants respectfully disagree that the '856 patent alone or in combination with the '162 patent renders the inventions of claims 80, 89, 103, 109, and 111 *prima facie* obvious under § 103. First, there is no suggestion or motivation to modify the teaching of the '856 patent to arrive at the invention of claims 80, 89, 103, 109, and 111. Specifically, the claims are directed to reducing the size or improving the appearance of a closed wound by topically administering a composition *consisting essentially of* a pharmaceutically acceptable carrier and a non-steroidal anti-inflammatory agent. In contrast, the '856 patent is directed to a *combination* of sulfasalazine (a nonsteroidal anti-inflammatory agent) and an effective amount of an antibody to an integrin. Further, the '856 patent explicitly teaches that the *antibody to the integrin* is the ingredient which is effective for treating a skin fibrosis (col. 3, ll. 65-67; col. 4, ll. 1-62; col. 14, ll. 1-3, 17-20). The '856 patent does not provide any motivation or suggestion to modify its teaching that the *combination* of an integrin antibody and sulfasalazine is effective for treating skin fibrosis. Moreover, there is no suggestion or motivation to not use the active ingredient, *i.e.* the integrin antibody, and instead use sulfasalazine *by itself* to treat a skin fibrosis. Indeed, according to the '856 patent, sulfasalazine is included in the composition only as an anti-inflammatory agent (col. 14, ll. 12).

Significantly, the '856 does not present *any* evidence that sulfasalazine can be used *by itself* to treat skin fibrosis. In fact, every example and claim of the '856 patent requires the use of an antibody or antibody fragment to an integrin. Thus, the '856 patent fails to provide any suggestion or motivation to modify the combination of antibody to antibody fragments to integrin with sulfasalazine as taught in the '856 patent. Moreover, based on the teachings of the '856 patent and the utter lack of a suggestion or motivation to use sulfasalazine by itself, one of ordinary skill in the art would not have a reasonable expectation of success in using sulfasalazine by itself to reduce the size or improve the appearance of a closed wound. Without a motivation or suggestion to modify the teachings of the '856 patent and without a reasonable expectation of success in achieving the invention of claims 80, 89, 103, 109, and 111, the '856 reference cannot be said to render the invention of claims 80, 89, 103, 109, and 111 *prima facie* obvious.

The combination of the '856 and '162 patents does not remedy the inadequacies of the '856 patent when it is taken alone. Specifically, the '162 patent does not even mention nonsteroidal anti-inflammatory agents. Rather, the '162 patent is directed to thermal insulating materials that may be used to increase the surface temperature of the skin. Therefore, the '162 patent does not itself provide motivation for modifying the teaching of the '856 patent to use salicylic acid *by itself* to reduce the size or improve the appearance of a "closed wound." The '162 patent also does not provide any *reasonable* expectation of success in reducing the size or improving the appearance of a closed wound by topically administering a composition consisting essentially of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent selected from the group listed, for example, in claim 80.

Moreover, to render a claimed invention obvious, the cited reference or combination of references must teach each and every element of the claimed invention. *See* MPEP § 2142. Neither the '856 patent, nor the '162 patent teaches or even suggests that any of the non-steroidal anti-inflammatory agents listed, for example, in claim 80 could be used *by itself* to reduce the size or improve the appearance of a "closed wound" as is required by claims 80, 89, 103, 109, and 111.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the '856 patent, either alone or in combination with the '162 patent. Applicants respectfully submit that pending claims 80, 89, 103, 109 and 111 are not rendered obvious by the '856 patent, alone or in combination with the '162 patent. This ground of rejection is overcome. Applicants respectfully request that it be withdrawn.

US 6,521,271 ('271) alone or in combination with US 5,552,162 ("'162")

Claims 80 and 103 stand rejected as allegedly unpatentable under 35 U.S.C. § 103 over the '271 patent. In particular, the Office action alleges that "US '271 suggests the treatment of scar[s] by topical application of the composition comprising NSAID." Page 7 of the Office action mailed 8 May 2006. Claims 80, 89, 103, 109, and 111 stand rejected as allegedly unpatentable under 35 U.S.C. § 103 over the '271 patent in combination with the '162 patent.

Applicants respectfully disagree that the '271 patent, alone or in combination with the '162 patent, renders the inventions of claims 80, 89, 103, 109 and 111 *prima facie* obvious under § 103. First, there is no suggestion or motivation to modify the teaching of the '271 patent to arrive at the inventions of claims 80, 89, 103, 109, and 111. Specifically, the claims are directed to a composition *consisting essentially of* a pharmaceutically acceptable carrier and a non-steroidal anti-inflammatory agent. In contrast, the '271 patent is directed to a *combination* of turmeric compounds and salicylic acid for reducing the size or improving the appearance of a scar. The '271 patent however, teaches that the tumeric compound is the ingredient which is effective for reducing the size or improving the appearance of a scar. Specifically, at col. 4, ll. 33-50 the '271 patent teaches that the *effectiveness* of *turmeric components* can be increased by administering turmeric components in combination with various alpha and beta-hydroxy acids, because the acids act as penetration enhancers:

> [I]t is believed that, when the turmeric component(s) are combined with alpha hydroxy acids, the effective concentration of the turmerin and curcumin provides a more active composition for treatment of scars, pigmentation and aging skin. It is believed that, when combined with

> alpha hydroxy acid, the component(s) of turmeric (in particular curcumin and turmerin) are able to penetrate the skin and have a pronounced effect on the skin being treated that would not be achieved in the absence of the alpha hydroxy acid.

Even further, in every example of the '271 patent, a turmeric compound is used as the active ingredient. There is no motivation in the '271 patent to use salicylic by itself, or as the active ingredient, for reducing the size or improving the appearance of a scar. Rather, the '271 patent teaches that salicylic acid is included in the composition because it is effective as a penetration enhancer or as an exfoliant. (col. 6, ll.22-26).

Indeed, the '271 patent particularly teaches that salicylic acid is a primary example of a hydroxy acid that functions as a penetration enhancer when used with a turmeric component (col. 4, ll. 48-49). In addition, at col. 9, ll. 4-9, the '271 patent teaches that salicylic acid "has been shown to aid in dead skin removal . . . and to have a keratinolytic effect that is useful for skin treatment." None of these characteristics of salicylic acid teach either expressly or inherently that salicylic acid is useful for reducing the size of or improving the appearance of a closed wound.

There is no motivation to modify this teaching of the '271 patent. Indeed, none of these characteristics of salicylic acid would motivate one of ordinary skill in the art to modify the teaching of the '271 patent (*i.e.* that turmeric compounds may be used to treat a scar) by using salicylic acid by itself or as the active ingredient to reduce the size or improve the appearance of a "closed wound."

Even further, the Lee Declaration submitted December 27, 2005 provides additional evidence that one of ordinary skill in the art would not be motivated to use salicylic acid, by itself, to reduce the size or improve the appearance of a closed wound as that term is used in the present claims. *See e.g.* paragraphs 31-48 of the Lee Declaration. As discussed more fully below, the Office action disregards the Lee Declaration as not relevant to evidence of nonobviousness. Applicants disagree. The Lee Declaration provides direct evidence of the knowledge of one of at least ordinary skill in the art

concerning salicylic acid and its application to treat closed wounds of the type claimed herein. According to MPEP § 2107, the Examiner "must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." (emphasis added). The Office action does not question the qualifications of Dr. Lee or the accuracy of the facts attested to in the Lee Declaration. Rather, the Office action improperly dismisses the declaration as irrelevant.

In addition to there being no motivation (either in the art or in the knowledge of those skilled in the art) to modify the teachings of the '271 patent to arrive at the claimed invention, none of the teachings in the '271 patent provide one of ordinary skill in the art with a *reasonable* expectation of success using a non-steroidal anti-inflammatory agent selected from the group listed, for example, in claim 80 to reduce the size or improve the appearance of a closed wound.

The '162 patent is relied on for the teaching of a thermal insulating hydrogel. Therefore, the '162 patent does not itself provide motivation for modifying the teaching of the '271 patent to use salicylic acid *by itself* to reduce the size or improve the appearance of a "closed wound." The '162 patent also does not provide any *reasonable* expectation of success in reducing the size or improving the appearance of a closed wound by topically administering a composition consisting essentially of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent selected from the group listed for example, in claim 80.

Moreover, to render a claimed invention obvious, the cited reference or combination of references must teach each and every element of the claimed invention. *See* MPEP § 2142. Neither the '271 patent alone nor in combination with the '162 patent teaches or even suggests that any of the non-steroidal anti-inflammatory agents listed, for example, in claim 80 could be used *by itself* to reduce the size or improve the appearance of a "closed wound" as is required by the claims of the present invention.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the '271 patent, either alone or in combination with the '162 patent. Applicants respectfully submit that pending claims 80, 89, 103, 109 and 111 are not rendered obvious by the '271 patent, alone or in combination with the '162 patent. Applicants respectfully request that this ground of rejection be withdrawn.

US 4,244,948 ("'948")

Claims 103 and 111 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over US 4,244,948. In particular, the Office action alleges US '948 teaches "a topical composition comprising esters of acetylsalicylic acid in amounts ranging from 1-10% in combination with a carrier comprising water and polyethylene glycol." Page 9 of the Office action mailed 8 May 2006.

Applicants respectfully disagree that the '948 patent renders the claimed invention obvious. In particular, the '948 patent — like DE '537 discussed below — is directed to methods of treating acne and does not disclose any methods of treating the closed wounds of claims 103 and 111 using non-steroidal anti-inflammatory inhibitors. The below discussion under the DE '537 heading explains why one of ordinary skill in the art would not be motivated to apply an acne treatment to treatment of the "closed wound" of claims 103 and 111. *See e.g.,* pages 18-21 below. This discussion also explains why one of ordinary skill in the art would not be have a *reasonable* expectation of success even if one were motivated to apply the acne treatment teachings of the '948 patent to a "closed wound" of claims 103 and 111. *See e.g.,* pages 18-21. Indeed, paragraphs 34-36, 38-42 of the Lee Declaration submitted December 27, 2005 (discussed more fully below) provide direct evidence that one of ordinary skill in the art would not be motivated to apply an acne treatment to treatment of the "closed wound" of claims 103 and 111. These paragraphs also clearly illustrate that even if one of ordinary skill in the art did apply an acne treatment to the "closed wound" of claims 103 and 111, one would not have a reasonable expectation of success in achieving a reduction in the size of the "closed wound" or an improvement in its appearance. For these reasons (more fully

discussed below) the '948 patent does not render claims 103 and 111 *prima facie* obvious. This ground of rejection is overcome and Applicants respectfully request it be withdrawn.

DE 27 07 537 (DE '537)

Claims 103 and 111 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over DE 27 07 537. In particular, according to the Office action, DE '537 teaches "formulations comprising salicylic acid in an amount of 1-3%, and carrier such as ethylene glycol." Page 10 of the Office action mailed 8 May 2006.

Applicants respectfully disagree that DE '537 teaches, suggests or provides any motivation for one of ordinary skill in the art to arrive at the claimed invention. Indeed, Applicants filed concurrently with the present application a PCT application (PCT/US01/08735), which was nationalized in the European Patent Office (the "EPO") as EP App. No. 01 918 824. The DE '537 reference was considered during prosecution of that corresponding EP application and the claims pending in EP App. were considered allowable over DE '537. Specifically, sheet 2 of the attached Examination Report (Communication pursuant to Article 96(2) EPC dated 15.06.2004) (Tab A) alleges that the claimed invention is not novel because DE '537 (D3) "relates to the use of salicylic acid for the treatment of hypertrophic scars." This is the same basis of rejection presented in the US. However, during prosecution of the EP application, Applicants overcame DE '537 because the teaching of that reference clearly is restricted to the treatment of acne scarring. Neither the claims in the EP application, nor the claims in the US application are directed at treating acne scarring. More specifically, DE '537 was overcome in the EP application based on the following arguments:

> Further, D3 is restricted to treatment of acne scarring. As amended herein, Claim 1 of the present application excludes any acne infection or scarring. Moreover, the role of salicylic acid in D3 is not defined. However, we submit that anyone skilled in the art would expect that a keratolytic agent, such as salicylic, (*sic*) acid would be useful to treat any sort of acne or similar skin infections. Indeed, acne related scarring can not be treated without first stopping the infection. Further, an ongoing acne infection is worsened by acne scarring,

> which further blocks the drainage of skin pores. Therefore, D3 correctly teaches that to treat acne skin scarring, one must first improve drainage of hair follicles and sebaceous glands entrapped in the scar. Salicylic acid is standard treatment for acne because it acts to decrease epithelial growth in response to inflammation or invention, thus it opens skin pores, improves drainage of skin pores and drains trapped bacteria. This is common knowledge in dermatology and is described in all dermatology textbooks. In contrast, for burn and trauma related scarring, to which Claim 1 of the present application is directed, there is no need to improve drainage of skin glands and hair follicles. Therefore it is not obvious that salicylic acid would be useful in treating post-burn or other post-trauma scarring. Therein lies the inventive step of the present invention. No one skilled in the art of acne treatment or medicine would expect that salicylic acid would treat or prevent post-trauma skin scars.

(Tab B). As stated above, claims nearly identical and arguably broader in scope than those currently pending in this US application (*see* Allowable EP claims, Tab D), are allowable over DE '537. *See* Tab C. Thus, allowance of the claims at Tab B in EP App. No. 01 918 824 over DE '537 is persuasive, objective evidence of the non-obviousness of the invention claimed in the present application.

Further, as previously argued, Applicants respectfully disagree that DE '537 renders the inventions of claims 103 and 111 *prima facie* obvious under the standards of 35 U.S.C § 103. First, there is no suggestion or motivation to modify the teaching of DE '537 to arrive at the invention of claims 103 and 111. Specifically, the claims are directed to reducing the size or improving the appearance of a closed wound having an intact epithelial surface. The claims are directed only to closed wounds selected from the group consisting of a wound caused by laceration; a wound caused by avulsion; a wound caused by burn; a wound caused by radiation; a wound caused by chemical facial peel; and a wound caused by accident, wherein the closed wound further consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar, or a fibrotic scar. In contrast, DE '537 is directed to treatment of acne. There is no motivation or suggestion either in DE '537 or in the art knowledge that would lead to applying the teachings of the DE 537 outside of *acne* scarring. In addition, there is no reasonable expectation of success that applying the teachings of DE 537 outside of acne scarring would reduce

the size or improve the appearance of a closed wound as that term is used in the claims. Further, DE 537 does not teach all the claim limitations of claims 103 or 111.

DE 537 is directed to treatment of acne, tinea versicolor, seborrheic dermatitis, and other disorders associated with hyperplasia that has been brought about by infected sebaceous glands. (Page 7, DE 537). There is no suggestion or motivation to apply the teaching of DE 537 to reduce the size or improve the appearance of a closed wound that is caused by laceration, avulsion, burn, radiation, chemical facial peel, or accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar, or a fibrotic scar. As explained more fully below, acne treatments, such as that described in DE 537, are directed at aiding in or promoting the removal or shedding of dead skin cells, whereas reduction in the size or improvement in the appearance of a closed wound as that term is used in the claims of the present invention is based on promoting cell growth.

An understanding of the etiology of acne and the mode of action of salicylic acid in acne treatments further demonstrates that there is no motivation to apply the teaching that salicylic acid can be used in an acne treatment to the types of closed wounds to which the claims are directed and also demonstrates there is no reasonable expectation of success in applying the teachings of DE 537 outside acne scarring. The declaration of Raphael C. Lee, M.D., Sc.D., submitted December 27, 2005 explains both the etiology of acne and the mode of action of salicylic acid in acne treatments.

The Office action however, concludes that the declaration is insufficient to overcome the rejection of the claims because "it include(s) statements which amount to an affirmation that the claimed subject matter functions as it was intended to function." Page 11 of the Office action mailed 8 May 2006. According to the Office action, the declaration is "not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof" nor is there any "showing that the objective evidence of nonobviousness is commensurate in scope with the scope of the claims." Page 11 of the Office action mailed 8 May 2006.

Applicants respectfully disagree that the Lee Declaration simply affirms that the claimed subject matter functions as intended. Applicants also respectfully disagree that the declaration is irrelevant to the issue of nonobviousness of the claimed subject matter. Indeed, the declaration provides direct evidence of how one of ordinary skill in the art would understand the cited references and their relationship to the claimed invention. Specifically, the declaration provides direct evidence of what one of ordinary skill in the art understood about use of salicylic acid in acne treatments. According to MPEP § 2107, the Examiner "must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." (emphasis added).

The CV attached to the Lee Declaration clearly demonstrates that Dr. Lee is a qualified expert and the Office action does not argue he is not. Further, the Office action does not question the accuracy of any facts discussed in the application. Rather, the Office action simply dismisses the declaration without acknowledging the significance of the facts attested to in that declaration. With specific regard to DE '537, Dr. Lee explains at paragraphs 34-36:

> 34. . . . It is commonly known and widely accepted that acne forms inside a skin pore as a result of abnormal desquamation of cells of the follicular epithelium. More specifically, a skin pore is an opening in the skin through which a very fine hair typically will grow and sweat glands will drain. Skin pores are connected to sebaceous glands, which produce an oily sebum that lubricates the hair and skin. Acne occurs when the sebaceous glands produce thick highly viscous oil that when combined with the desquamated cells, forms a plug that obstructs further drainage of sebum. This results in an enlarged, blocked pore called a comedo. Plugged pores create a breeding ground for skin bacteria. As the bacteria flourish in the comedo, skin infection begins leading to pain, inflammation, and scarring.
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> 35. Existing acne treatments focus on *slowing* down the skin's production of oil, and *encouraging* rapid desquamation (*e.g.* shedding of dead skin cells), or *fighting* bacteria. Increasing desquamation leads to larger diameter skin pores and thinner epidermis and better drainage of the pore.

36. More specifically, salicylic acid is lipid soluble, which means it can penetrate into a pore containing sebum and loosen desquamated skin cells built up inside the pore. Indeed, it is well understood and widely accepted in the art that salicylic acid treats acne by loosening the intercellular cement material present in the pores, increasing the diameter of the skin pore, and by thinning the epidermis, which drains the plugged pores and prevents further plugs from forming. By draining the skin pores and removing the infection, inflammation and fibrous tissue formations are reduced. Thus, any treatment that would cure acne would also *indirectly* prevent acne scaring. *See e.g.,* Davies, M. and Marks, R. "Studies on the effect of salicylic acid on normal skin." *Br. J. Dermatol.* 1976. 95(2):187-92 and Roberts *et al.,* "Detection of the action of salicylic acid on the normal stratum corneum." *Br. J. Dermatol.* 1980. 103(2):191-6.

Significantly the Lee Declaration provides direct evidence that Dr. Lee, as one of at least ordinary skill in the art, would not expect that "salicylic acid could be used to treat either an external wound, including one that has reepithelialized, or a scar caused by an external trauma" based on the teachings of DE '537 and the level of knowledge and skill in the art at the time of the invention. (Paragraph 37, Lee Declaration). This is direct evidence of nonobviousness — *i.e.,* direct evidence that there is no motivation, either in the art or in the DE 537 reference to apply the teachings of DE '537 (*e.g.,* that salicylic acid can be used to treat acne) to reduce the size or improve the appearance of a "closed wound."

The Lee Declaration further provides direct evidence that even if one of ordinary skill in the art were motivated to apply the teachings of DE '537 to treat a "closed wound," such a person would not have a *reasonable* expectation of success. According to Dr. Lee, it is well-known that salicylic acid should not be used on wounds with a weakened external barrier, such as wounds that have recently re-epithelialized, because use of salicylic acid on inflamed, irritated, or infected areas of the skin can cause severe irritation. *See* paragraphs 38-42 of the Lee Declaration, which reference Rhein *et al.,* "Targeted delivery of salicylic acid from acne treatment products into and through skin: role of solution and ingredient properties in relationships to irritation." *J. Cosmet Sci.* 2004. 55(1):65-80 and USP DI Advice for the Patient [Internet]. [Greenwood Village (CO)]: Thomson MICROMEDEX; ©2005. Salicylic acid; [revised 2005 Jan 19; cited

2005 October 7]; [~ 8 p.]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202516.html (attached).

As explained at paragraph 38 of the Lee Declaration, one of ordinary skill in the art would expect that salicylic acid would cause severe irritation of the skin if the salicylic acid was administered when the epidermal barrier was weakened or lost, as happens with external wounds such as the closed wounds to which claims 103 and 111 are directed. Indeed, the Lee Declaration evidences the nonobviousness of the claimed invention, stating, "one of ordinary skill in the art in 2001 would expect salicylic acid to delay the wound healing process, irritate and exacerbate, not alleviate, scarring in skin tissues that are in recovery from an external trauma." (Paragraph 39, Lee Declaration). *See also* paragraph 29 of the Lee Declaration (discussing the Lee, KH "Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." J Pharm Sci. 1968 Jun;57(6):1042-3 reference, which teaches that topical application of a composition comprising 3% salicylic acid *retards* the wound healing process).

Thus, one of ordinary skill in the art would neither be motivated to use salicylic acid to treat a closed wound, nor would such a person have a *reasonable* expectation of success in using salicylic acid to reduce the size or improve the appearance of a "closed wound."

Moreover, DE '537 does not disclose all elements of claims 103 or 111 because DE 537 does not disclose either a kit or reducing the size or improving the appearance of any closed wound caused by laceration; by avulsion; by burn; by radiation; by chemical facial peel; or by accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar or a fibrotic scar.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the DE '537 reference. Hence, given the additional objective evidence of nonobviousness based on allowance of the EP claims over DE '537, Applicants respectfully submit that neither claim 103 nor claim 111 is obvious in view of DE '537. Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants believe that currently pending Claims 80, 89, 103, and 109 and 111 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

C. Noel Kaman

C. Noel Kaman
Registration No. 51,857
Attorney for Applicant

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200